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UTILITY PATENT
APPLICATION TRANSMITTAL LETTER

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Enclosed for filing is the utility patent application of Jipin Zhong and David Greenspan for BIOACTIVE SOL-GEL COMPOSITIONS AND METHODS.

Also enclosed are:

[X] 15 sheet(s) of [ ] formal [X] informal drawing(s);

[ ] a claim for foreign priority under 35 U.S.C. §§ 119 and/or 365 in [ ] a separate document [ ] the Information Sheet;

[ ] a certified copy of the priority document;

[ ] ____ verified statement(s) claiming small entity status;

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The declaration of the inventor(s) [X] also is enclosed [ ] will follow.

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Independent Claims	8	MINUS 3 =	5	x $80 =	400.00
If multiple dependent claims are presented, add $260.00					-0-
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APPLICATION FOR UNITED STATES LETTERS PATENT

of

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for

BIOACTIVE SOL-GEL COMPOSITIONS AND METHODS

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BIOACTIVE SOL-GEL COMPOSITIONS AND METHODS

FIELD OF THE INVENTION

The present invention relates to bioactive glass compositions, for example, used for filling bone defects, and bioactive compositions produced by a sol-gel process. The present invention also relates to various methods for making sol-gel bioactive glasses and methods of treatment using bioactive glasses.

BACKGROUND OF THE INVENTION

Sol-gel processes for making bioactive glass using sol-gel technology are generally known. For example, U.S. Patent No. 5,074,916 (the "'916 patent"), the subject matter of which is incorporated herein by reference, discloses sol-gel processing techniques used to produce alkali-free bioactive glass compositions based on SiO_2, CaO and P_2O_5. The '916 patent discloses that by varying the SiO_2 content, a range of hydroxyapatite production rates can be obtained. Also, varying the time of exposure to actual or simulated in vivo solutions permits use of a range of allowable proportions of SiO_2. The sol-gel derived compositions disclosed in the '916 patent can be chosen to achieve target values for a thermal expansion coefficient, elastic modulus and volume electrical resistivity.

The processes and compositions described in U.S. Patent No. 5,074,916 have certain disadvantages. For example, the process of the '916 patent does not provide for bioactive glasses having large pore sizes. This results in a relatively low rate of

hydroxycarbonate apatite ("HCA") development when the glasses are exposed to biological fluids and tissues. See "Effect of Texture on the Rate of Hydroxyapatite Formation on Gel-Silica Interface", J. Am. Ceram. Soc., 78[9] 2463-68 (1995), the subject matter of which is herein incorporated by reference. Moreover, the resultant product lacks homogeneity, stability and can only be heated to a limited extent during preparation. Also, the resultant product lacks an acceptable level of resorbability.

Other examples of sol-gel processes can be found in Thomas, "Multicomponent Glasses From the Sol-Gel Process", Noyes Publications edited by Lisa C. Klein of the Center for Ceramics Research, College of Engineering, Rutgers, Piscataway, New Jersey and "Sol-Gel Science - The Physics and Chemistry of Sol-Gel processing, Brinker et al., Academic Press Inc. These publication are also incorporated by reference.

Previous methods for preparing monoliths of bioactive glasses have also proven unsatisfactory. Earlier methods required the use of various toxic chemicals in an effort to avoid cracking of the monolith during drying. U.S. Patent No. 4,849,378 ("the 378 patent"), incorporated herein by reference discloses a method of fabricating an ultraporous silicon dioxide containing gel monolith having a predetermined mean pore size by controlling temperature, duration and other conditions of aging. The '378 patent discloses that the use of a drying control chemical additive is important and formamide is the additive of choice. Similarly, U.S. Patent No. 4,851,150 ("the '150 patent") addresses drying control chemical additives for rapid production of large sol-gel derived monoliths. The '150 patent also discloses drying in a methanolic atmosphere. Both of these methods are unsatisfactory because they require the use of chemical additives.

Other early work in U.S. Patent No. 5,076,980 (incorporated by reference) used drying under humidity environment and sintering under some gas atmosphere to make a

sol-gel monolith. However, the focus of such procedures was the fabrication of crack-free and fully dense silica glass and the pore texture of the monolith was not mentioned. Moreover, this patent does not address the preparation of a bioactive glass.

Accordingly, it is an object of the present invention to provide a sol-gel process, particle and monolith that yield bioactive glasses used for bone grafting and filling osseous defects, having larger pore size at a given level of silicon dioxide in the final composition, faster HCA formation, better resorbability, and better homogeneity. It is further an object of the present invention to provide for precise control of rates of resorbtion.

SUMMARY OF THE INVENTION

The present invention is directed to a process for making bioactive glasses used, for example, for bone grafting including; preparing a reaction mixture (sol) capable of forming a gel, aging the reaction mixture, near equilibrium drying a gel resulting from the reaction mixture, and heating the near equilibrium-dried gel. The present invention is also directed to dried bioactive glass compositions and monolithic bioactive compositions having improved resorbability. The present invention is further directed to materials suitable for bone grafting, repairing of tissue defects and other orthopedic uses.

BRIEF DESCRIPTION OF THE DRAWINGS

FIGURE 1 Surgically created defect 8 weeks post-op. Very little bone formation noted.

FIGURE 2 Melt derived 45S5 Bioglass® at 4 weeks. Red stains show bone formation throughout the defect, especially around particles near the edges of the defect (arrow).

FIGURE 3 Melt derived 45S5 Bioglass® at 8 weeks, showing dramatic increase in bond formation, evenly throughout defect. Some resorption of particles is occurring.

FIGURE 4 58S sol-gel glass produced by near-equilibrium drying at 4 weeks post-op. Rapid bone formation is noted even in the center of the defect (solid arrows). Resorption of many particles can already be seen (open arrows).

FIGURE 5 58S sol-gel glass at 8 weeks. Extensive bond formation is noted throughout the defect. Most of the particles have already resorbed, and are replaced by newly maturing trabecular bone.

FIGURE 6 77S sol-gel produced by near-equilibrium drying at 4 weeks post-op. Bone formation is present, but not as extensive as in 58S glass. Arrows indicate resorption of some particles.

FIGURE 7 77S sol-gel glass produced by near-equilibrium drying at 8 weeks. Bone formation has proceeded to the center of the defect (red stained regions). About 50% of the particles have resorbed.

FIGURE 8 58S sol-gel glass at 8 weeks post-op. Red stained region shows extensive bone formation around and even inside a particle which is clearly resorbing (region labeled at "A"). No inflammatory response is noted.

FIGURE 9 77S sol-gel glass at 8 weeks post-op. Bone is noted surrounding particles with no inflammatory response. Resorption of particles can be noted (arrows) although it is slower than in the 58S sol-gel glass.

FIGURE 10 FTIR spectra of various sol-gel bioactive glass compositions. All have formed extensive HCA layers.

FIGURE 11(A) FTIR spectra of sol-gel bioactive glass prepared by previous method A.

FIGURE 11(B) FTIR spectra of sol-gel bioactive glass made in accordance with the present invention including a near equilibrium drying step. As seen in the spectra, more rapid formation of HCA is observed when near equilibrium drying is used.

FIGURE 12 FTIR spectra of sol-gel bioactive glass monolith after 24 hours in SBF using near equilibrium drying.

FIGURE 13 An example of a drying schedule showing temperature vs. time in standard vs. near equilibrium drying schedules.

FIGURE 14 Example of a heating schedule showing temperature vs. time.

FIGURE 15 Silica release of particle prepared in accordance with the present invention vs. a previous sol-gel method disclosed in the '916 patent.

FIGURE 16 Diagram of average pore size vs. drying temperature.

FIGURE 17 A phase diagram of water.

FIGURE 18 Ion release of 77(s) in SBF.

FIGURE 19 Si release of 77S(B) in SBF.

DETAILED DESCRIPTION OF THE INVENTION

The present invention includes a process for making bioactive glasses in a sol-gel process used for filling osseous defects including a near equilibrium drying step which provides for increased pore size and bioactivity in the final product. The present invention also includes sol-gel bioactive glass compositions. The present invention further relates to materials suitable for bone grafting and repairing of tissue defects where the rate of resorption can be precisely controlled.

As referred to herein, bioactive glasses are typically silicon dioxide based compositions capable of forming HCA when exposed to physiological fluids. Typically, bioactive glasses have the following composition by weight percentage:

SiO_2	-	40 - 90
CaO	-	4 - 45
Na_2O	-	0 - 10
P_2O_5	-	2 - 16
CaF_2	-	0 - 25
B_2O_3	-	0 - 4
K_2O	-	0 - 8
MgO	-	0 - 5

The process of the present invention includes a drying step which is not included in earlier processes. It has unexpectedly been determined that the use of near-equilibrium drying in place of or in addition to drying under dry conditions used in prior processes provides for much larger average pore size in the final composition at a given level of SiO_2 than previously known. It was unexpectedly found that a near equilibrium drying resulted in larger pore size and a higher rate of resorption.

Near-equilibrium drying is drying under the conditions near the two phase boundaries in the phase diagram at a temperature and pressure sufficient to yield a bioactive glass with large pore structure i.e. a pore structure sufficient to yield a bioactive glass. For example, near equilibrium drying may be drying under the conditions near the line in the phase diagram of water as shown in Fig. 17 (or other liquids such as methanol, ethanol, acetone, liquid CO_2, benzene and so on). By manipulating the sealing of the designed drying chamber to adjust the extent of the drying condition away from the equilibrium line and relative humidity (from environment humidity to 98%), the duration of near-equilibrium drying, and the temperature at which the drying is conducted, one can

drastically alter pore size of resultant bioactive glass. For example, increasing the sealing of the drying chamber during drying typically results in an increase in relative humidity and pore diameter. Near-equilibrium drying temperature can also be varied, for example, as depicted in Figure 13 for the case of water drying. If using other liquids mentioned above than water, one may obtain a faster drying or increase the pore size range of the gel to a large extent.

By manipulating the percentage humidity, the duration of near equilibrium drying, and the temperature at which near equilibrium drying is conducted, one can drastically alter pore size of the resultant bioactive glass. For example, increasing the level of humidity during drying typically results in an increase in pore diameter. Near equilibrium drying temperatures can also be varied, for example, as depicted in Figure 13. It was unexpected that the change in drying temperature should give rise to such a large change in pore structure and an increase in resorbability.

A sol-gel process in accordance with the present invention is any process that includes the use of a sol-gel in the preparation of bioactive glass. For example, a reaction mixture including tetraethoxysilane (TEOS), triethylphosphate (TEP), and calcium nitrate can be used to make sol-gel bioactive glasses. Alkoxides of calcium, titanium, zirconium, magnesium aluminum, iron and potassium can also be used. Other appropriate ingredients will also be apparent to those of ordinary skill in the art. The present invention also contemplates the use of aerogels. When an aeorogel is used, increased pressure is used instead of near equilibrium drying to achieve larger pore size and greater resorbability.

Sol-gel processing in accordance with the present invention includes a near equilibrium drying step which yields larger pore size in the final product and permits

development of HCA very rapidly for both high and low silicon dioxide content gels. Indeed, compositions in accordance with the present invention form HCA more rapidly than prior gels when exposed to SBF (Simulated Body Fluid, Kokubo, T. et al., J. Biomed. Mater. Res., 24, 721-34, 1990) or physiological fluids. The near equilibrium drying technique of the present invention also provides for more homogeneous gels which can be heated to higher temperatures than previous gels while retaining large pore diameter. This permits much better control of the final product e.g. resorbability, homogeneity and physical structure. For example, previous sol-gel compositions were not able to provide adequate resorbability at higher levels of silicon dioxide. Surprisingly, the present invention provides for excellent resorbability even when high amounts of silicon dioxide are included. The sol-gel glasses of the present invention are also more homogeneous than prior sol-gel glasses and calcium is distributed uniformly.

The process of the present invention also provides for bioactive glass capable of resorbing more quickly than known sol-gel bioactive glass materials. For example, in-vivo testing of one embodiment of the present invention showed that more than 50% of sol-gel material made in accordance with the process of the present invention resorbed at eight weeks (see Figures 5, 7, 8 and 9). Comparable prior 45S5 melt derived bioactive glasses, as described in the '916 patent which allow bone ingrowth to about the same extent, have not resorbed at all by eight weeks. Indeed, the '916 patent indicates glasses including more than 55% silicon dioxide are not bioactive. Moreover, bioactive glass made by the process of the present invention also exhibits substantially no unwanted inflammatory response.

The drying technique of the present invention can be used to prepare all types of sol-gel bioactive glasses. For example, the process of the present invention can be used to prepare frit, monoliths, powders, coatings, fibers, mats, weaves and composites.

Generally, frit, monoliths, powders, and coatings can be derived from sol-gel processing. Frit can be ground to very broad ranges of particle size such as from about 2 μm up to 1 mm for any purpose. The monolith can be formed to complex shapes such as various implants. Powders can be made to spherical form and from submicron to a few hundred microns. Such compositions are useful, for example, in bone repair and other orthopedic applications, drug delivery, treating tooth hypersensitivity as well as the remineralization of tooth structure, burn healing, and wound healing.

While not being bound to any particular theory, it is believed that the near-equilibrium drying step reduces capillary force inside the pore structure of the gel which results in large pore size. Gels are networks of small colloid particles. The networks includes voids which become pores and pore channels in the final glass composition. It is believed that the moisture of the near-equilibrium drying step enhances the reaction at the neck between two particles in the network and the strength of the neck and "back bone" of the gel structure which reduces shrinkage of the drying structure and ultimately results in gels with large pores.

On the other hand, due to the liquid tension, the pressure difference between the different size of pores and channels is:

$$\Delta P = 2\gamma\cos\theta / r$$

where, γ is liquid tension, θ is contact angle and r is the radius of pores and pore channels. During drying, the pressure difference, ΔP, will pull the network tight enabling

pore collapse and gel shrinkage as liquid evaporates. It is believed that near-equilibrium drying allows the liquid inside the pore structure to evaporate under the condition of near-equilibrium at any temperature in Fig. 13. This keeps liquid vapor pressure inside the channels and pores at high heating conditions which resists the shrinkage and collapse of the gel structure and results in large pore sizes.

The following examples are included for purposes of illustration only. They are not intended to narrow the scope of the claims in any way.

Example I - Preparation of Sol-gel Frit

The preparation of sol-gel bioactive glass frit was accomplished as follows:

First, a reaction mixture of deionized water, TEOS, TEP, and calcium nitrate was prepared. Deionized water and hydrochloric acid solutions were combined in a large reactor container. The container was placed on a stirring plate and the solution was stirred using a magnetic stirring bar at medium speed. Then, TEOS was poured into the container and allowed to mix until the solution went clear. The mole ratio of water vs. the mole ratio of TEOS was 4 (other mole ratios can be used e.g. 2 - 16). After 30 minutes, TEP was added to the stirring solution. In another 20 minutes, calcium nitrate was added. The solution was then stirred for an additional hour then followed by the below steps to make frit:

a. The reaction mixture was transferred to large containers and the containers were placed in an oven for aging at 60°C for 54 hours;

b. Pore liquor was removed and the aged gels were transferred into a large drying vessel and the vessel was placed inside a designed drying chamber with a proper amount of water. Then, the whole chamber was placed into an oven and dried under the drying schedule in Figure 13;

c. The dried gels were then heated in a large quartz crucible using the heating schedule of Figure 14;

d. After drying and heating, the gel cracks and forms large granules. The granules can then be ground to form frit and then separated into various size ranges thus obtained.

The following compositions were prepared by a process including a near equilibrium drying step:

Sample ID	Si mol%(wt%)	Ca mol%(wt%)	P mol%(wt%)
77S	80 (77)	16 (14)	4 (9)
68S	70 (68)	26 (23)	4 (9)
58S	60 (58)	36 (33)	4 (9)

The foregoing compositions were prepared from reaction mixtures prepared as follows:

Sample 77S:

1)	D.I. Water:	Xx237 ml	
2)	HCl (2N):	Xx44.89 ml	mix 10 minutes
3)	TEOS ($Si(OC_2H_5)_4$):	Xx667 ml	mix 30 minutes
4)	TEP ($OP(OC_2H_5)_3$):	Xx5l ml	mix 20 minutes
5)	$Ca(NO_3)_2*4H_2O$:	X x 141.24 g	mix 60 minutes

Sample 68S

1)	D.I. Water:	Xx238.66 ml	
2)	HCl (2N):	Xx39.78 ml	mix 10 minutes
3)	TEOS ($Si(OC_2H_5)_4$):	Xx663.55 ml	mix 30 minutes
4)	TEP ($OP(OC_2H_5)_3$):	Xx58 ml	mix 20 minutes
5)	$Ca(NO_3)_2*4H_2O$:	Xx260.93 g	mix 60 minutes

Sample 58S

1)	D.I. Water:	Xx377.42 ml	
2)	HCl (2N):	Xx62.28 ml	mix 10 minutes
3)	TEOS ($Si(OC_2H_5)_4$)	Xx511.19 ml	mix 30 minutes
4)	TEP ($OP(OC_2H_5)_3$):	Xx52.10 ml	mix 20 minutes
5)	$Ca(NO_3)_2*4H_2O$:	Xx324.80 g	mix 60 minutes

X = Any factor to increase batch size.

x = multiply

Comparison of regular drying with near equilibrium drying schedules:

As can be seen in Fig. 13, the drying temperature is 180°C for standard drying techniques and, in example, 130°C for near equilibrium drying of the present invention. The use of lower temperatures in near equilibrium drying maintains higher humidity for a longer period of time (gels can be humidity dried by steam injection into a drying oven). Lower near equilibrium drying temperature also benefits the reaction between necks and strengthens structure.

Near equilibrium drying:

Total drying time was 72 hours as shown in fig. 13. The proper amount of water was placed in the oven to provide water vapor which maintained humidity around 98% in the first 60 hours at 60°C, 90°C and 130°C. In the last 12 hours at 130°C, the humidity was decreased gradually from 98% to ambient humidity as water evaporates out.

Comparative Results:

The following results were obtained for near equilibrium dried samples made in accordance with the present invention with heating at 700°C:

Sample	% SiO_2	Average Pore Diameter	Surface Area (M^2/g)
58S	60	86	207
68S	70	65	305
77S	80	40	389

The following results were obtained when the near equilibrium drying step of the present invention is omitted (the process of U.S. Patent No. 5,074,916) with heating at 700°C:

Sample	% SiO_2	Average Pore Diameter	Surface Area (M^2/g)
58S	60	68	289
68S	70	50	326
77S	80	24 (30)	241(431)

( ) = sample heated at 600°C

As seen above, the near equilibrium drying step of the present invention provides for an unexpected increase in pore size. As further illustrated below, this results in a drastic and

unexpected improvement in bioactivity i.e. the ability to form HCA when exposed to *in vivo*.

In Vivo Bone Implantation

Figures 1-9 are photographs indicating the excellent results obtainable by the present invention when compared with other bioactive glasses when exposed in vitro or in vivo. Figure 1 shows what a surgically created defect looks like 8 weeks post-op. Figures 2 and 3 show the results obtained when melt derived bioactive glasses are used. Figures 4-9 show the excellent results obtained by the sol-gel of the present invention. Figure 6 shows resorption in high silica content particles (80% by weight) after only 4 weeks in *in vivo*. Figure 7 shows 50% resorption of 80% silica content particles after only 8 weeks in *in vivo*. Even more dramatic results can be seen in Figures 4 and 5 which show extensive resorption in 60% by weight silica bioactive glass compositions after only 4 weeks in *in vivo* and very advanced resorption after only 8 weeks. This animal model included near equilibrium dried particles in accordance with the present invention of 300-800 microns as measured by optical spectroscopy. The photos of figures 1-9 are rights to histological sections from the animal study.

In Vitro Exposure SBF

Other resorbability testing was also conducted on the foregoing comparative sol-gels.

0.2g of sol-gel bioactive glass particles of samples 77S(A) [no near equilibrium drying] and 77S(B) [equilibrium dried] were tested in 200 ml of SBF in a centerfuge at 175 RPM over a duration of 1hr, 6hrs, 20hrs, 7 days, 14 days and 28 days. Gel particles with large pore size show greater degradability than small pore size as demonstrated in

Figure 15. 77S(A) had an average pore diameter of 24 angstroms whereas 77S(B) had an average pore diameter of 40 angstroms. As shown in Figure 18, silica continues to leach from the glasses and calcium and phosphate precipitate back on the particles which simulates the events happening after implantation that induce bone growth while silica dissolves. The negative release of calcium and phosphorous in Figure 18 implies that calcium and phosphorous precipitate from solution to particles. Thirty percent by weight of silica has been lost in 4 weeks as shown in Figure 19 which means that these are certainly bioresorbable materials.

FTIR DATA

FTIR spectra are used to indicate the formation of HCA on the surface of bioactive glasses that have been exposed to simulated or real body fluids. Figure 10 shows that samples prepared by a process including near equilibrium drying developed HCA within 24 hours. Figures 11(A) and (B) show the FTIR spectra of 77S(A) in accordance with the '916 patent vs. 77S(B) made by a process including near equilibrium drying. It took 2 days to form HCA on the surface of the 77S(A) sample whereas it only took 14 hours to form HCA on the 77S(B) sample which included a near equilibrium drying step.

Example 2 - Preparation Of A Monolith

Monoliths must be prepared in a manner that minimizes crack formation. In order to accomplish the manufacture of monoliths of bioactive sol-gel glasses without cracks, others have prepared monoliths by drying under supercritical conditions (C. Jeffrey

Brinker, George W. Scherer, "Sol-Gel Science, the Physics and Chemistry of Sol-Gel Processing", Academic Press, 1990) or with chemical additives (L.L. Hench "Science of Ceramic Chemical Processing", pp. 52-64, Wiley 1986). In the present example, an inexpensive method, drying under near equilibrium conditions was used. Water vapor pressure associated with near equilibrium drying yields large pore gels and strengthens the backbone of colloid particle networks to prevent cracking during drying. The resultant bulk monoliths show great bioactivity as seen in Figure 12. Unlike drying under higher pressure supercritical conditions, near equilibrium drying does not require the use of expensive, complicated equipment. Bioactive aerogels can also be used to prepare monoliths by replacing the near equilibrium drying step with higher pressure. Near equilibrium drying also does not require the use of drying chemicals or high chemical removal temperatures as required by chemical drying additives.

Monoliths were prepared by the following process:

A reaction medium was prepared including deionized water, hydrochloric acid (2N), TEOS, TEP, and calcium nitrate. First, deionized water and hydrochloric acid were combined in a large reaction container and placed on a stirring plate. The solution was stirred using a magnetic stirring bar at medium speed. TEOS was then poured into the container and the solution was allowed to mix until clear. The mole ratio of water to TEOS was 4 (the mole ratio can be varied from, for example, 2 - 16). After 30 minutes, TEP was added to the stirring solution. In another 20 minutes, calcium nitrate was added. The solution was then stirred for an additional hour then followed by the following steps to make monoliths:

a. The prepared solutions were cast into molds of desired shape and loosely sealed. The molds were then placed in a closed chamber with water for aging for a period of 1 - 7 days at room temperature;

b. The molds were then sealed tightly and placed in an oven for aging for 54 hours at 60°C;

c. The pore liquor was then removed from the molds and the shaped gel was quickly transferred into a large drying vessel with a loosely fit cover placed over it. Then, the vessel was placed inside a designed drying chamber with a proper amount of water and the whole chamber was placed into an oven and dried using the drying schedule in Figure 13;

d. The dried gels were then heated in a quartz crucible using the heating schedule in Figure 14.

We claim:

1. A process for making bioactive glasses comprising:

preparing a reaction sol capable of forming a sol-gel;

aging said reaction mixture;

near equilibrium drying a gel resulting from the reaction mixture, and;

heating the near equilibrium dried gel at a temperature above ambient.

2. The process of Claim 1, further comprising grinding the near equilibrium dried gel.

3. The process of Claim 2, further comprising classifying the ground near equilibrium dried gel to various particle size ranges.

4. The process of Claim 1, said aging conducted at a temperature of at least about 40°C.

5. The process of claim 1, said aging conducted for a duration of at least about 35 hours.

6. The process of Claim 1, said near equilibrium drying conducted at about 60 to 98% humidity.

7. The process of Claim 1, said near equilibrium drying conducted at a temperature of between about 130°C to about 180°C over at least part of the duration of the near equilibrium drying step.

8. The process of Claim 1, said near equilibrium drying conducted at temperatures varied over time between about 130°C to about 180°C.

9. The process of Claim 8, said near equilibrium drying conducted at a temperature ramp with a positive time vs. temperature slope over at least part of the duration of said near equilibrium drying step.

10. The process of Claim 1, the heating step conducted at between about 200°C to about 700°C over at least part of the duration of the heating step.

11. The process of Claim 1, the heating step conducted at temperatures varying over time between 200°C to about 700°C over at least part of the duration of the heating step.

12. The process of Claim 11, the heating step conducted at a temperature ramp with a positive time vs. temperature slope over at least part of the duration of said heating step.

13. The process of Claim 1, the reaction mixture including water, hydrochloric acid, tetraethoxysilane, triethylphosphate, or calcium nitrate, or mixtures thereof.

14. A near equilibrium dried bioactive glass comprising a silicon dioxide based composition prepared by a sol-gel process capable of forming hydroxycarbonate apatite layer when exposed to physiological fluids.

15. The bioactive glass of Claim 14, said glass having an average pore size greater than about 60A° when the silicon dioxide content of the bioactive glass is in the range of about 55 to about 65% by weight.

16. The bioactive glass of Claim 14, said glass having an average pore size greater than 70A° where the silicon dioxide content is in the range of about 65 to about 75% by weight.

17. The bioactive glass of Claim 14, said glass having an average pore size greater than 30A° when the silicon dioxide is in the range of about 75 to about 85% by weight.

18. A near equilibrium dried bioactive glass composition comprising a silicon dioxide based composition having a pore size greater than a corresponding non-near equilibrium-dried bioactive glass.

19. A process for making bioactive glasses by a sol-gel process, the improvement comprising near equilibrium drying a sol-gel.

20. The process of Claim 19, wherein said near equilibrium drying is accomplished at about 60 to 98% humidity.

21. The process of Claim 19, the improvement further comprising near equilibrium drying at a temperature up to about 150°C.

22. The process of Claim 19, the improvement further comprising near equilibrium drying at an initial temperature of less than about 100°C and a final temperature of less than about 150°C.

23. A near equilibrium-dried bioactive glass comprising, by weight %:

SiO_2	-	40 - 90
CaO	-	4 - 45
Na_2O	-	0 - 20
P_2O_5	-	2 - 10
CaF_2	-	0 - 25
B_2O_3	-	0 - 10

and a surface area greater than the non-near equilibrium-dried bioactive glass having an identical composition.

24. The near equilibrium-dried bioactive glass of Claim 23 wherein said near equilibrium-dried bioactive glass has a surface area of greater than about 175m^2/g and a silicon dioxide content of about 55 to 65% by weight.

25. The near equilibrium-dried bioactive glass of Claim 23, wherein said near equilibrium-dried bioactive glass has a surface area of greater than about 250 m^2/g and a silicon dioxide content of about 65 to 75% by weight.

26. The near equilibrium-dried bioactive glass of Claim 23, wherein said near equilibrium-dried bioactive glass has a surface area of about 300 m^2/g and a silicon dioxide content of about 75 to 85% by weight.

27. A sol-gel process for making a bioactive glass monolith comprising:

preparing a reaction mixture capable of forming a bioactive sol-gel monolith;

casting the reaction mixture into a mold of desired shape;

aging said reaction mixture cast in said mold at a temperature elevated above ambient;

near equilibrium drying the reaction mixture, and;

heating the reaction mixture.

28. The process of Claim 27, wherein the reaction mixture comprises deionized water, hydrochloric acid, nitric acid, tetraethoxysilane, triethylphosphate or calcium nitrate or mixtures thereof.

29. The process of Claim 27, further comprising conducting a pre-aging step before said aging, wherein said pre-aging comprises aging the reaction mixture at ambient temperature.

30. The process of Claim 27, further comprising removing a pore liquor after said aging and before said near equilibrium drying.

31. A near equilibrium-dried sol-gel monolith comprising the product of the process of Claim 27.

32. A method for treating orthopedic defects comprising contacting an orthopedic defect with an defect healing amount of near equilibrium dried sol-gel bioactive glass.

33. A composition for the treatment of orthopedic conditions comprising a bioactive sol gel glass capable of forming an HCA layer within 12 hours of exposure to simulated body fluids.

34. The composition of claim 33, wherein said glass is capable of forming an HCA layer within 5 hours of exposure to simulated body fluids.

35. The composition of claim 33, wherein said glass is capable of forming an HCA layer within 2 hours of exposure to simulated body fluids.

36. The composition of claim 33, wherein said glass is more than 50% resorbed 8 weeks after implantation into a patient.

37. The composition of claim 33, wherein said glass further comprises at least 77% silicon dioxide.

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ABSTRACT OF THE DISCLOSURE

A process for making bioactive glasses is described including preparing a reaction mixture of reactants capable of forming a sol-gel, aging the reaction mixture, near equilibrium drying a gel resulting from the reaction mixture, and heating the -near equilibrium-dried gel described. Also described are near equilibrium-dried bioactive glass compositions.

COMBINED DECLARATION AND POWER OF ATTORNEY FOR UTILITY PATENT APPLICATION	Attorney's Docket No. 028870-056

As a below-named inventor, I hereby declare that:
My residence, post office address and citizenship are as stated below next to my name;
I BELIEVE I AM THE ORIGINAL, FIRST AND SOLE INVENTOR (if only one name is listed below) OR AN ORIGINAL, FIRST AND JOINT INVENTOR (if more than one name is listed below) OF THE SUBJECT MATTER WHICH IS CLAIMED AND FOR WHICH A PATENT IS SOUGHT ON THE INVENTION ENTITLED:

BIOACTIVE SOL-GEL COMPOSITIONS AND METHODS

the specification of which

(check one) ☒ is attached hereto;

☐ was filed on _____ as

Application No. _____

and was amended on _____; (if applicable)

I HAVE REVIEWED AND UNDERSTAND THE CONTENTS OF THE ABOVE-IDENTIFIED SPECIFICATION, INCLUDING THE CLAIMS, AS AMENDED BY ANY AMENDMENT REFERRED TO ABOVE;

I ACKNOWLEDGE THE DUTY TO DISCLOSE TO THE OFFICE ALL INFORMATION KNOWN TO ME TO BE MATERIAL TO PATENTABILITY AS DEFINED IN TITLE 37, CODE OF FEDERAL REGULATIONS, Sec. 1.56 (as amended effective March 16, 1992);

I do not know and do not believe the said invention was ever knownor used in the United States of America before my or our invention thereof, or patented or described in any printed publication in any country before my or our invention thereof or more than one year prior to said application; that said invention was not in public use or on sale in the United States of America more than one year prior to said application; that said invention has not been patented or made the subject of an inventor's certificate issued before the date of said application in any country foreign to the United States of America on any application filed by me or my legal representatives or assigns more than twelve months prior to said application;

I hereby claim foreign priority benefits under Title 35, United States Code Sec. 119 and/or Sec. 365 of any foreign application(s) for patent or inventor's certificate as indicated below and have also identified below any foreign application for patent or inventor's certificate on this invention having a filing date before that of the application(s) on which priority is claimed:

COMBINED DECLARATION AND POWER OF ATTORNEY	Attorney's Docket No. 028870-056

COUNTRY/INTERNATIONAL	APPLICATION NUMBER	DATE OF FILING (day, month, year)	PRIORITY CLAIMED
			YES_ NO_
			YES_ NO_

I hereby appoint the following attorneys and agent(s) to prosecute said application and to transact all business in the Patent and Trademark Office connected therewith and to file, prosecute and to transact all business in connection with international applications directed to said invention:

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I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

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(1/96)

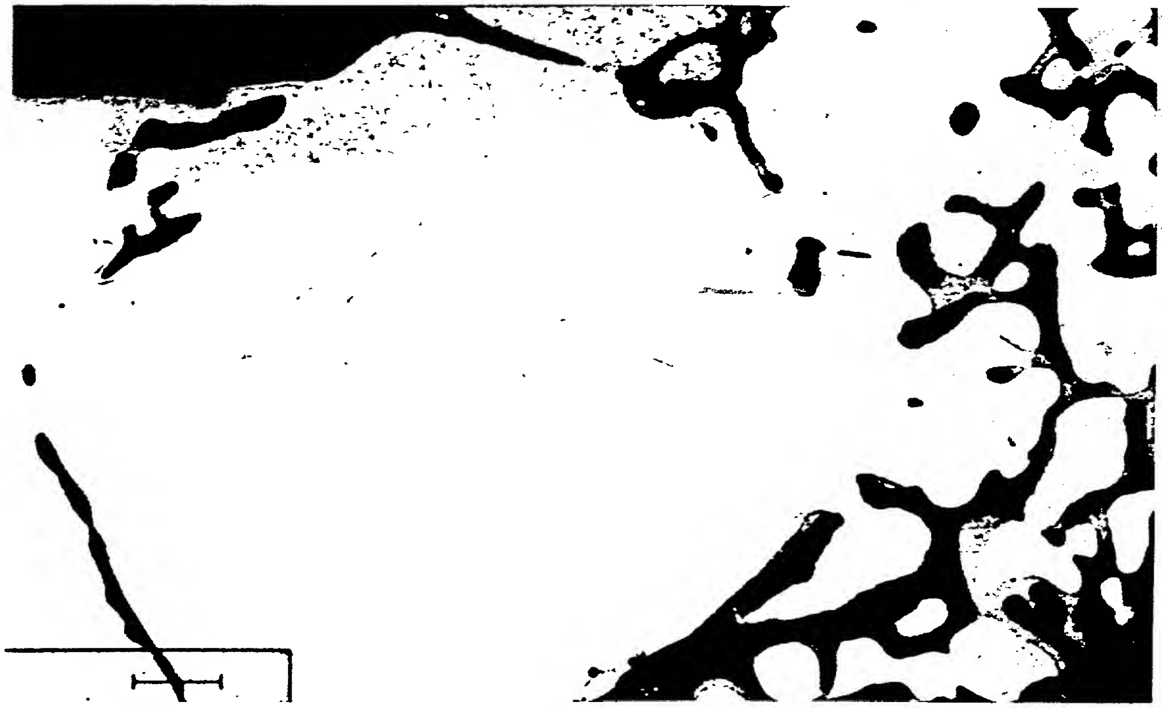


Figure 1

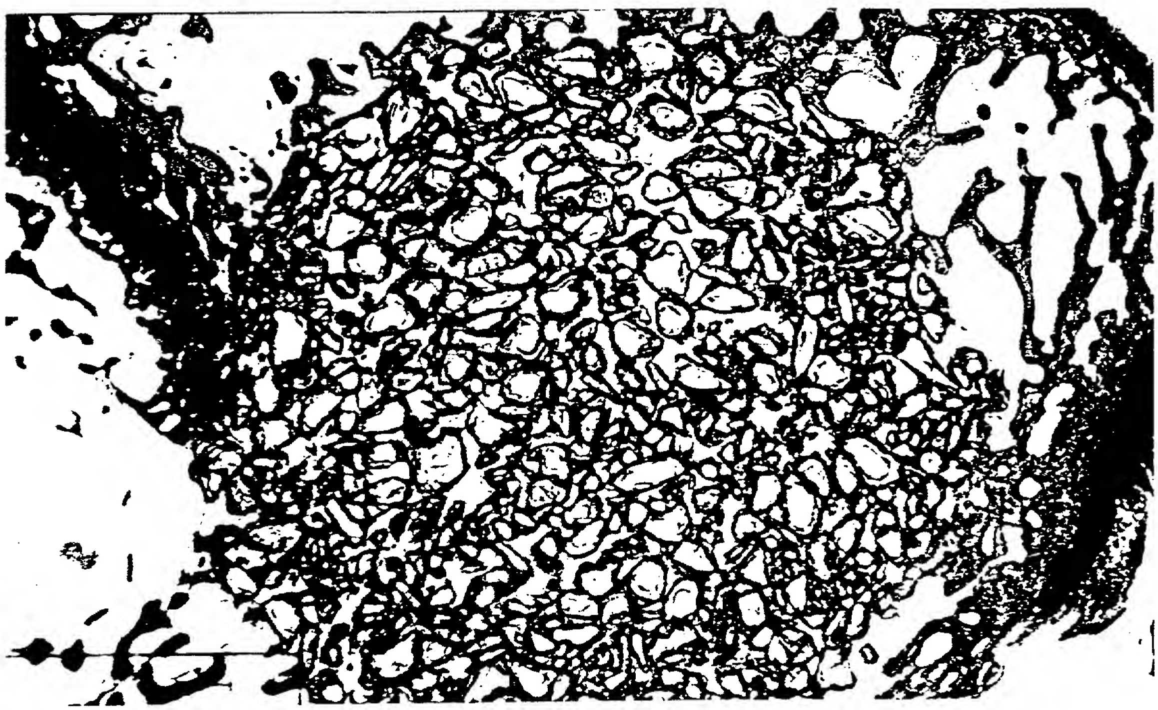
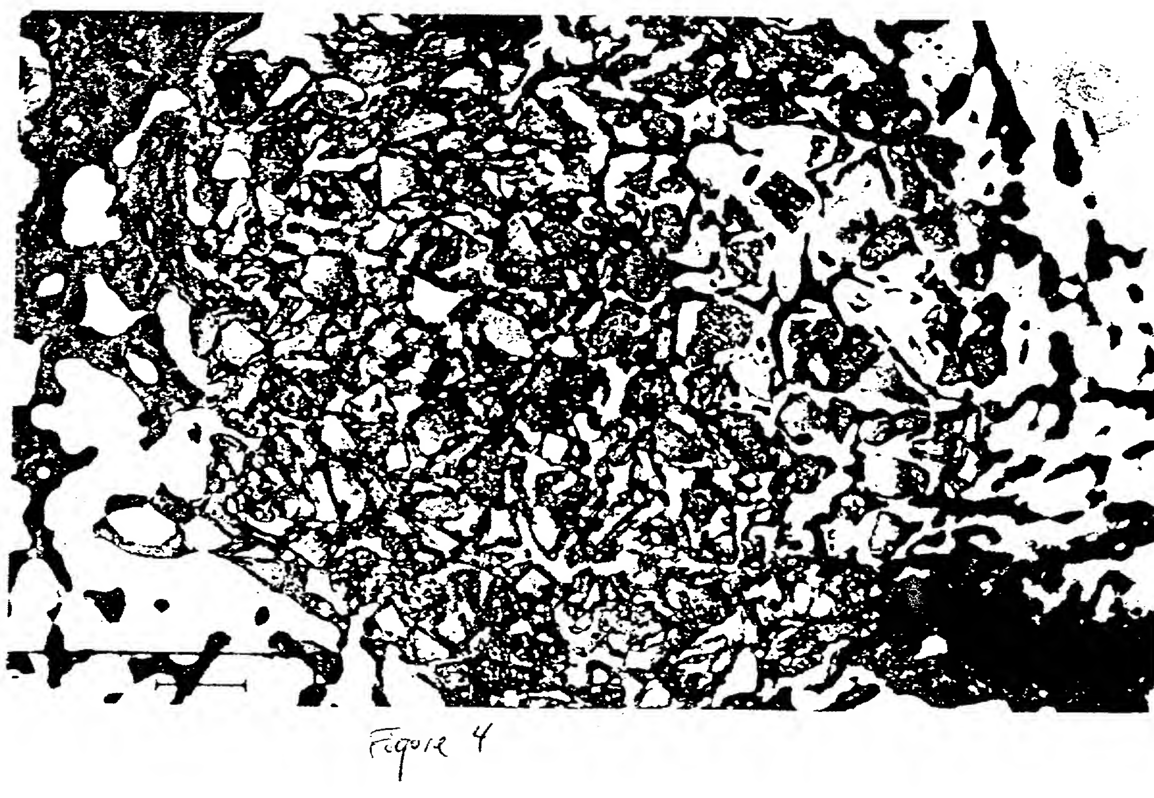


Figure 2

Figure 3



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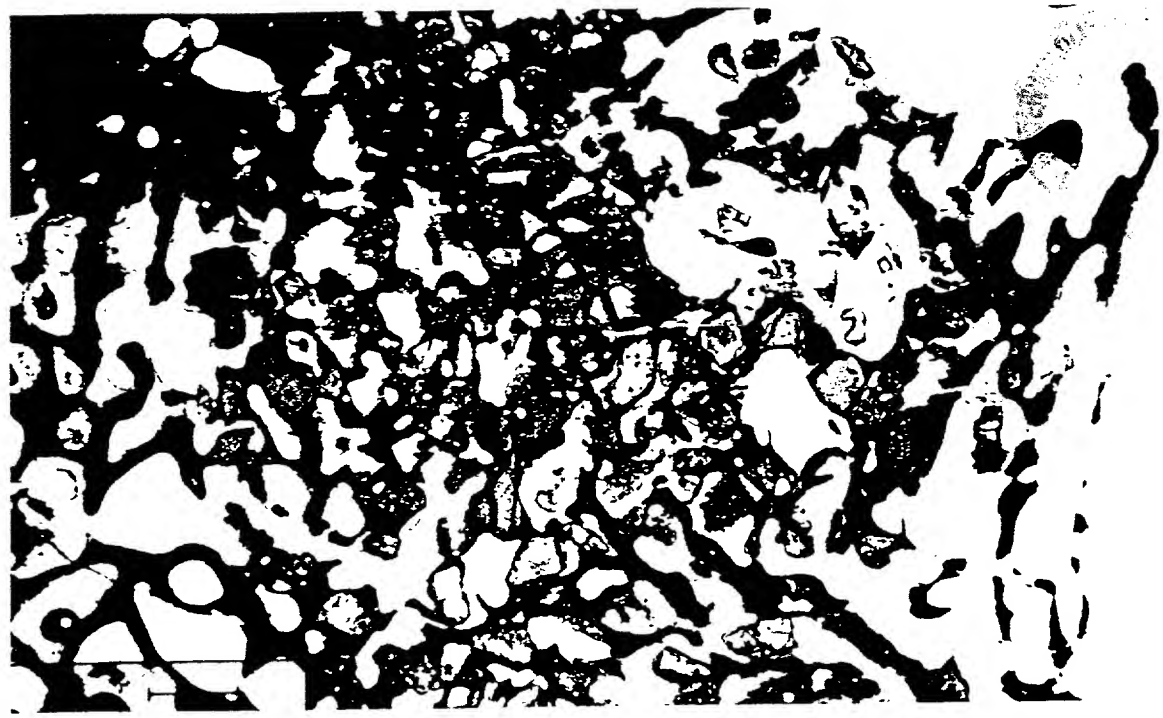

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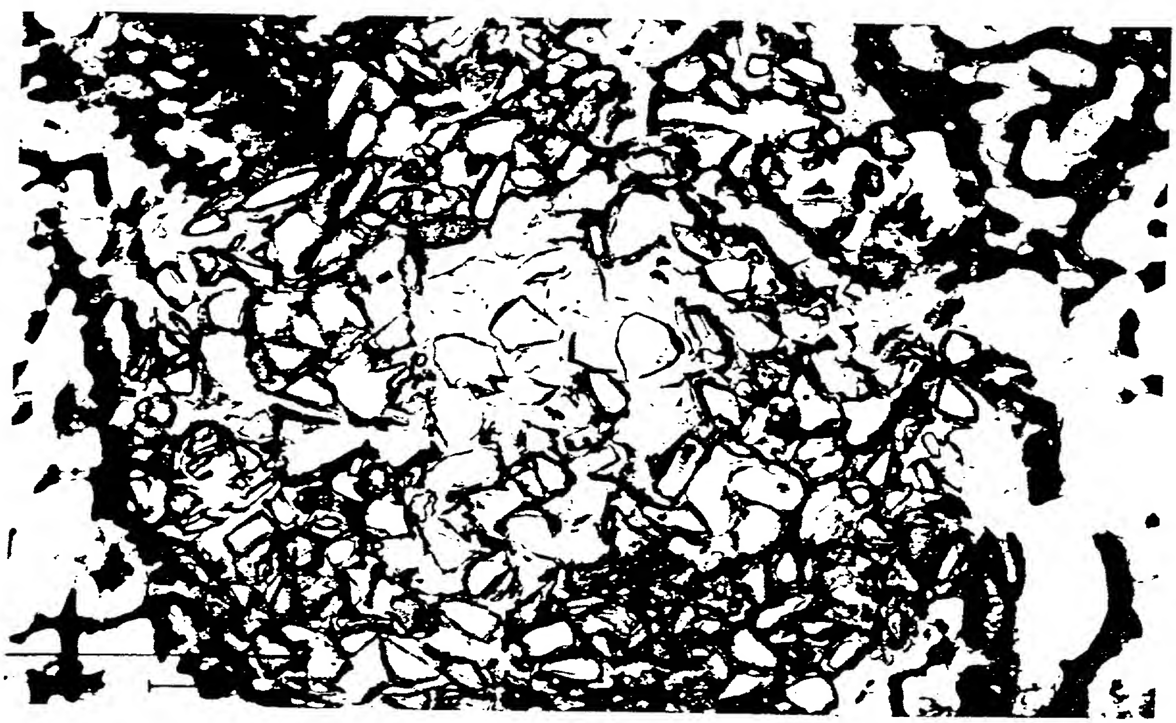
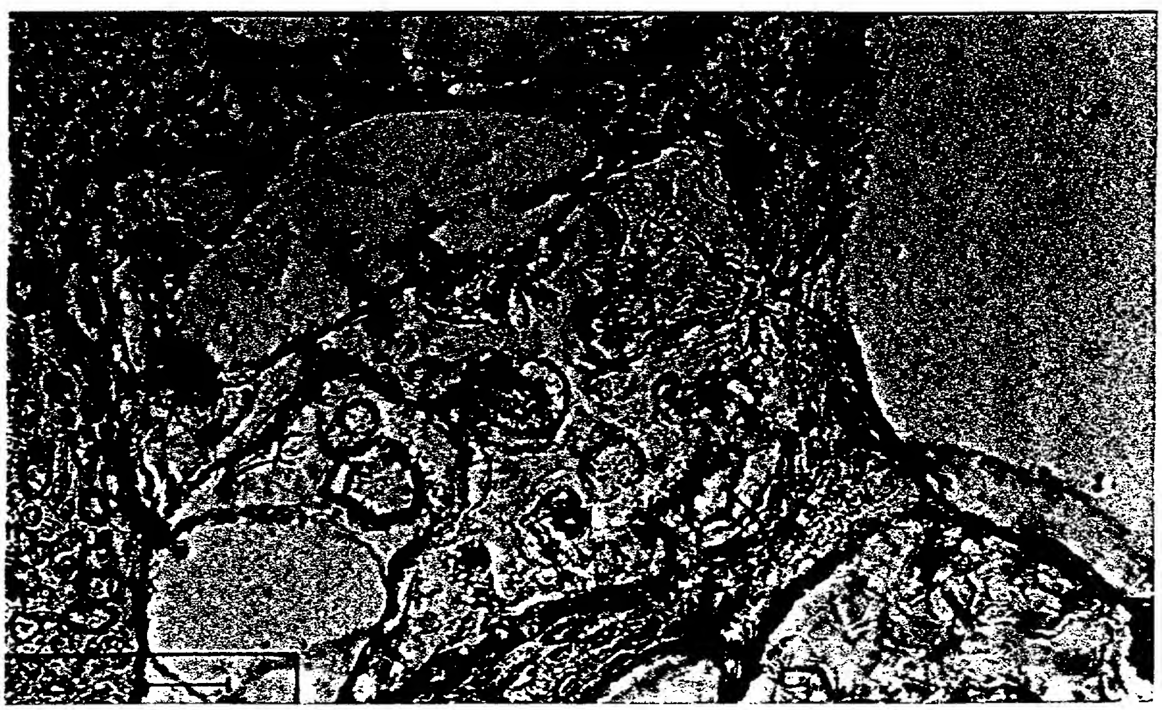


Figure 6

Figure 7



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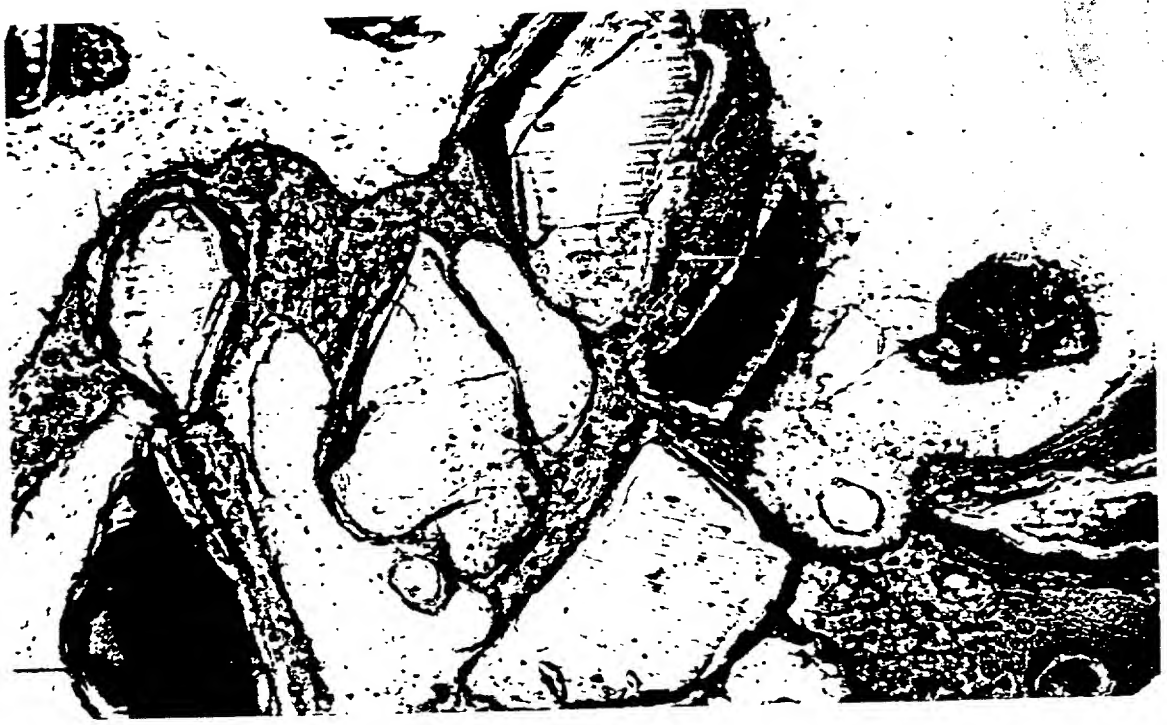

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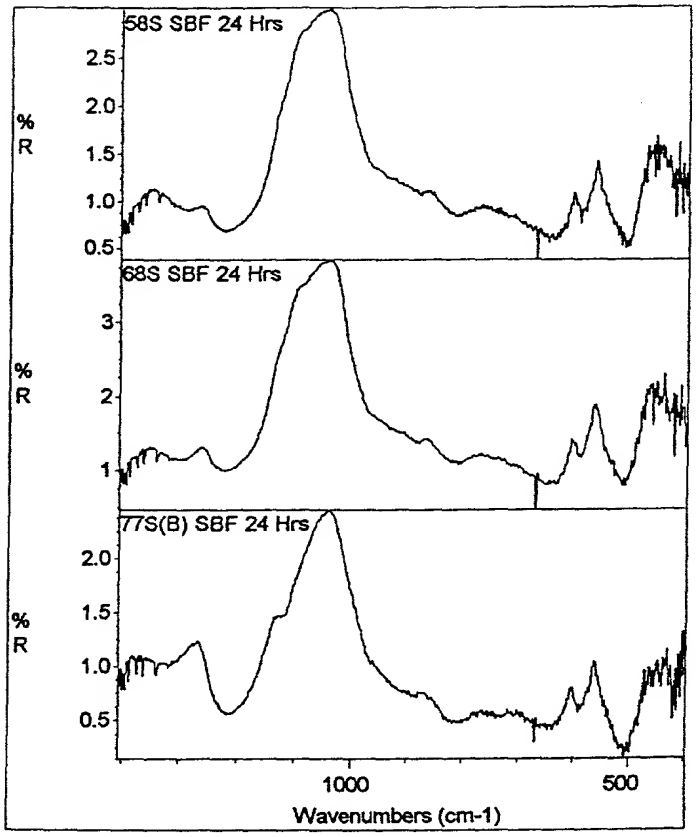
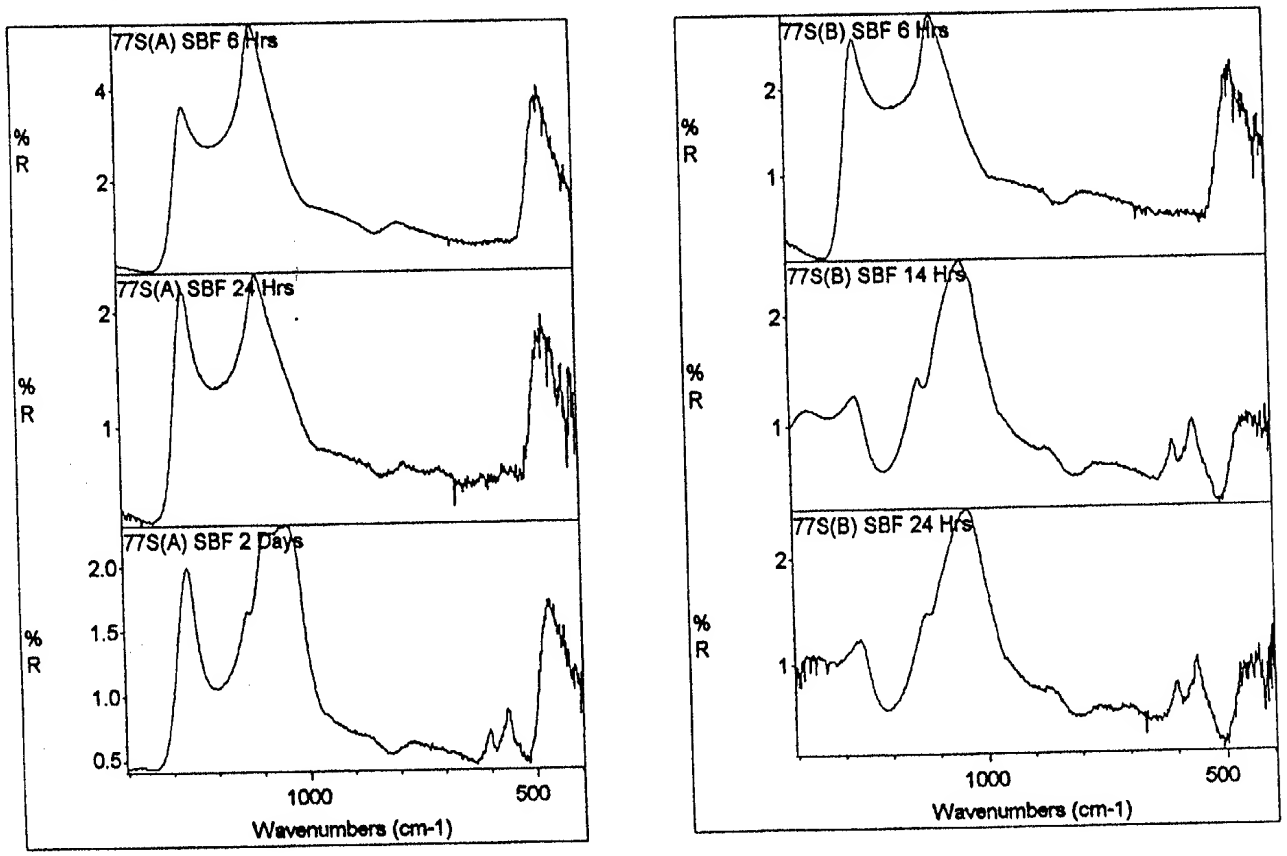


Fig. 1 FTIR Spectra of Sol-Gel Bioglasses in SBF 24 Hours

16



(A) (B)

Fig. 11 FTIR Spectra of Sol-Gel Bioglass Made by Previous Method (A) and by Near-equilibrium Drying(B) in SBF at Various Times

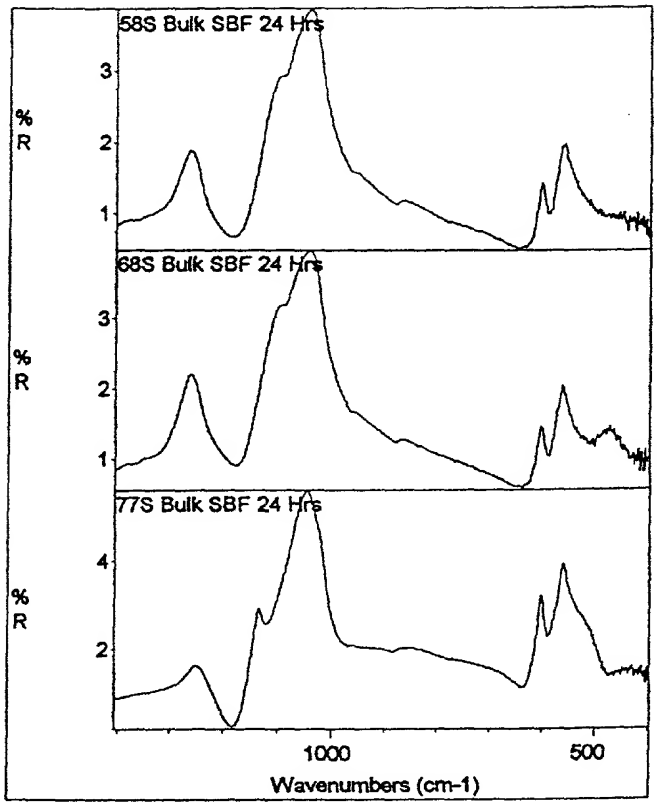
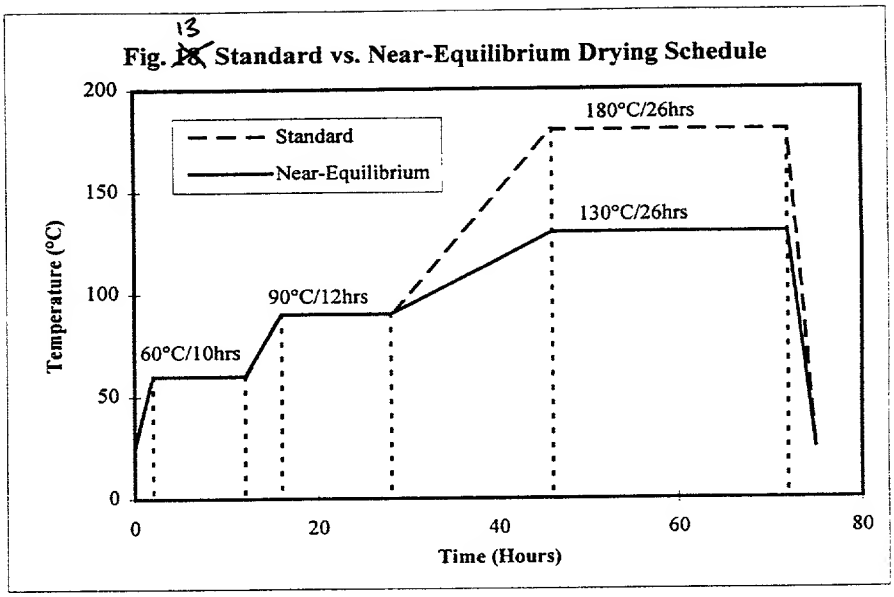


Fig. 3 FTIR Spectra of Sol-Gel Bioglass Monolith in SBF 24 Hours

Fig. ~~18~~ 13 Standard vs. Near-Equilibrium Drying Schedule



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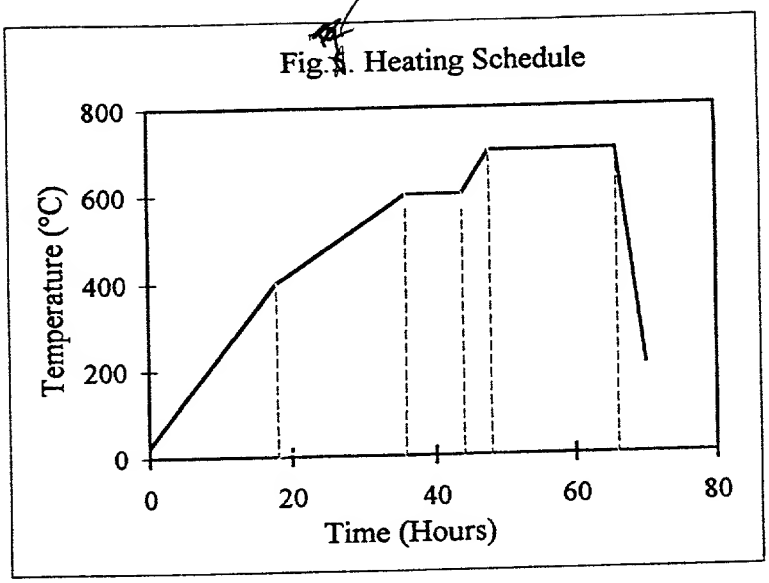

Fig. 1. Heating Schedule

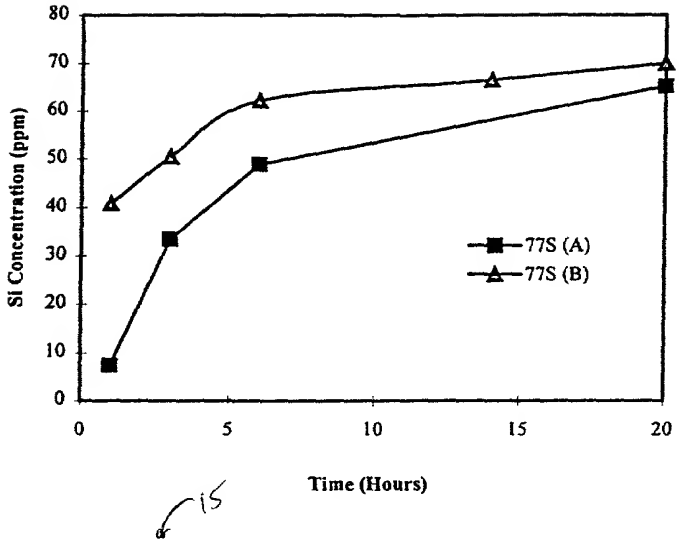

Fig. 8 Si Release of Two Particle Size of 77S

16

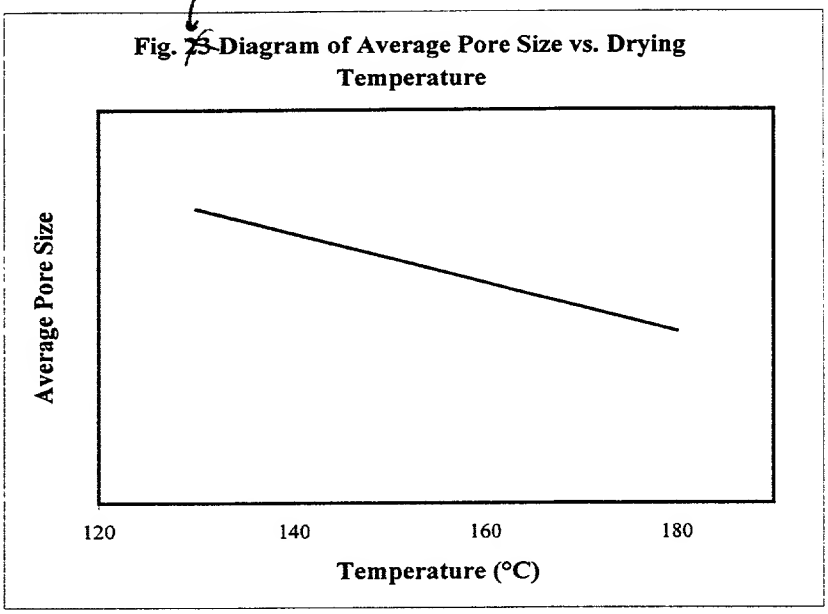

Fig. ~~23~~ 16 Diagram of Average Pore Size vs. Drying Temperature

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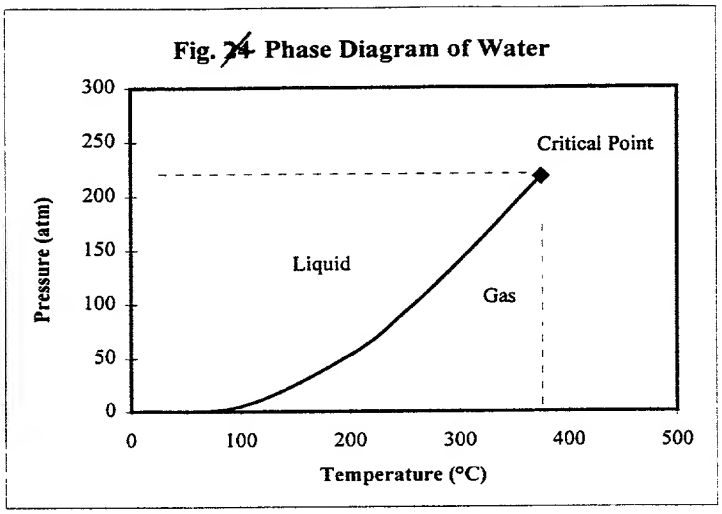
Fig. 24 Phase Diagram of Water



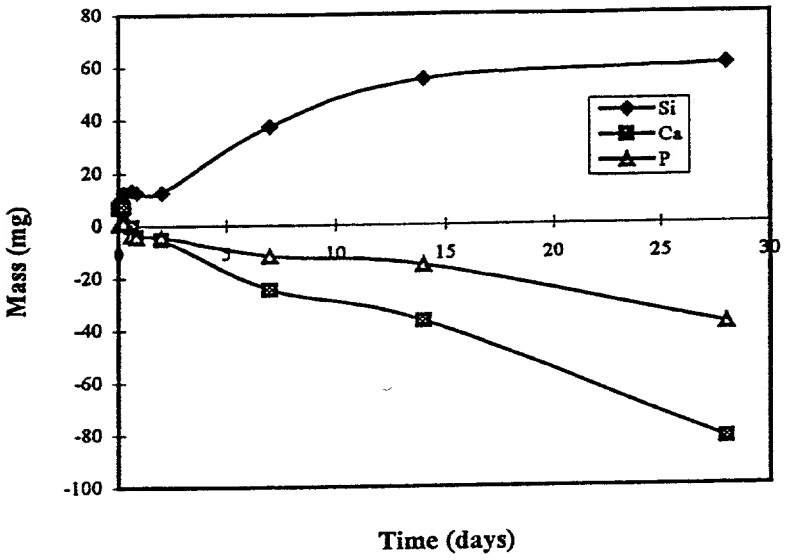


Fig. 1 Ion Release of 77S(B) in SBF

18

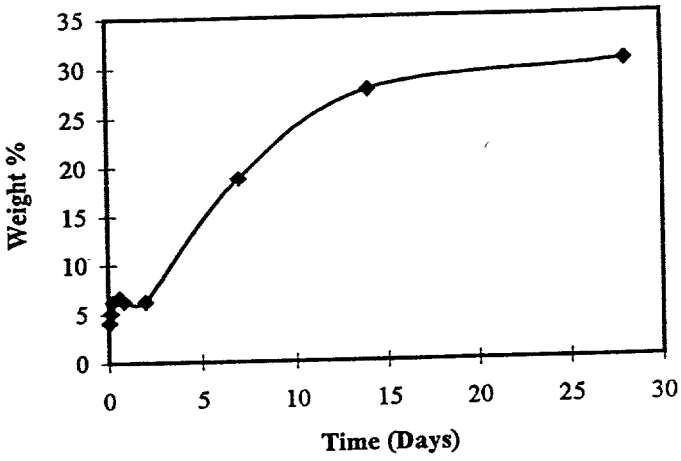


Fig. 8 Si Release of 77S(B) in SBF